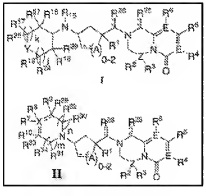
DETAILED ACTION

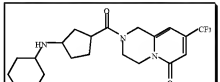
Status of the Claims / Priority

Claims 1-27 are pending in the current application. This application is a 35 U.S.C. § 371 National Stage Filing of International Application No. PCT/US2005/002454, filed January 26, 2005, which claims priority under 35 U.S.C. § 119(e) to US Provisional Application No. 60/539,691, filed January 28, 2004.

Restrictions / Election of Species

Applicant's provisional election of the following, with traverse, in the reply filed on September 30, 2009, is acknowledged: a) Group I - claims 1-24; and b) substituted pyrido[1,2-*a*]pyrazinone of formula I/II - *undisclosed*, shown right below, and hereafter referred to as 2-(3-(tetrahydro-2*H*-pyran-4-ylamino)cyclopentanecarbonyl)-8-(trifluoromethyl)-3,4-dihydro-1*H*-pyrido[1,2-*a*]pyrazin-6(2*H*)-one, where j = 1; k = 1; Y = -O-; A = $-CH_2-$; R^1 = -H; R^2 = -H; R^3 = -H; R^4 = -H; R^5 = $-CF_3$; R^6 = -H; R^{15} = -H; R^{16} = -H; R^{17} = -H; R^{18} = -H; R^{19} = -H; R^{24} = -H; R^{25} = -H; R^{26} = -O-; R^{27} = -H; R^{28} = -H; R^{29} = -H; **E = -C-**; **E = -C-**; and **Z = -C-**. Claims 1-7, 11-18, 20-22 and 24 read on the elected species. Affirmation of this election must be made by applicant in replying to this Office action.





Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse. See MPEP §

818.03(a).

The requirement is still deemed proper and is therefore made FINAL.

The elected species, shown above, was found to be free of the prior art. Thus, the examiner has expanded the forthcoming prosecution to include all claims relevant to the genus of Group I, for a first Office action and prosecution on the merits.

Claims 25-27 were withdrawn from further consideration, pursuant to 37 CFR 1.142(b), as being drawn to a nonelected or cancelled invention, there being no allowable generic or linking claim.

Thus, a first Office action and prosecution on the merits of claims 1-24 is contained within.

Claim Objections

Claims 1, 4-24 are independently objected to because of the following informalities: the claims lack compliance with the *Requirement for Restriction / Election of Species*, mailed on September 1, 2009, and discussed herein above in the section entitled *Restrictions / Election of Species*. Appropriate correction is required.

Claim 1 is further objected to because of the following informalities: *independently* should be inserted before *selected*, with respect to R^{29} and R^{33}. Appropriate correction is required.

Claim 19 is further objected to because of the following informalities: *wherein* should be inserted before R^{16}. Appropriate correction is required.

Claim 23 is objected to because of the following informalities: any claim may contain

tables *only if* the subject matter of the claim makes the use of tables desirable; in the instant case, the use of the table is deemed undesirable and should be removed, with only species being recited, separated by a comma or semicolon between each species. Appropriate correction is required. See MPEP § 11.10.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Substituted pyrido[1,2-a]pyrazinones and pharmaceutical compositions of the formula I/II

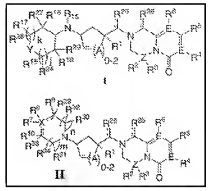
Claims 1-22 and 24 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for substituted pyrido[1,2-*a*]pyrazinones and pharmaceutical compositions of the formula I/II, where j = 1; k = 1; A = -CH_2-; Y = -O-; R^1 = -H or -C_{1-6}alkyl; R^5 = -H, -F, -Cl, -Br or -C_{1-6}alkyl; R^6 = -H, -F, -Cl, -Br or -C_{1-3}alkyl; R^{25} = -H or -C_{1-6}alkyl; R^{26} = -(=O); m, n and X, together with the nitrogen to which they are attached, form a pyrrolyl ring; and no combination of R^7, R^8, R^9, R^{10}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33} and R^{34}, forms a ring, does not reasonably provide enablement for substituted pyrido[1,2-*a*]-pyrazinones and pharmaceutical compositions of the formula I/II, where j ≠ 1; k ≠ 1; A ≠ -CH_2-; Y ≠ -O-; R^1 ≠ -H or -C_{1-6}alkyl; R^5 ≠ -H, -F, -Cl, -Br or -C_{1-6}alkyl; R^6 ≠ -H, -F, -Cl, -Br or -C_{1-3}alkyl; R^{25} ≠ -H or -C_{1-6}alkyl; R^{26} ≠ -(=O); m, n and X, together with the nitrogen to which they are attached, do not form a pyrrolyl ring; and any combination of R^7, R^8, R^9, R^{10}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33} and R^{34}, forms a ring. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and/or use the invention commensurate in scope with these claims. Substituted pyrido[1,2-*a*]pyrazinones and pharmaceutical compositions of the formula I/II, where $j \neq 1$; $k \neq 1$; $A \neq -CH_2-$; $Y \neq -O-$; $R^1 \neq$ -H or -C_{1-6}alkyl; $R^5 \neq$ -H, -F, -Cl, -Br or -C_{1-6}alkyl; $R^6 \neq$ -H, -F, -Cl, -Br or -C_{1-3}alkyl; $R^{25} \neq$ -H or -C_{1-6}alkyl; $R^{26} \neq$ -(=O); m, n and X, together with the nitrogen to which they are attached, do not form a pyrrolyl ring; and any combination of R^7, R^8, R^9, R^{10}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33} and R^{34}, forms a ring, as recited in claim 1, have not been adequately enabled in the specification to allow any person having ordinary skill in the art, at the time this invention was made, to make and/or use substituted pyrido[1,2-*a*]pyrazinones and pharmaceutical compositions of the formula I/II, where $j \neq 1$; $k \neq 1$; $A \neq -CH_2-$; $Y \neq -O-$; $R^1 \neq$ -H or -C_{1-6}alkyl; $R^5 \neq$ -H, -F, -Cl, -Br or -C_{1-6}alkyl; $R^6 \neq$ -H, -F, -Cl, -Br or -C_{1-3}alkyl; $R^{25} \neq$ -H or -C_{1-6}alkyl; $R^{26} \neq$ -(=O); m, n and X, together with the nitrogen to which they are attached, do not form a pyrrolyl ring; and any combination of R^7, R^8, R^9, R^{10}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33} and R^{34}, forms a ring.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is *undue*. These factors include, but are not limited to: (a) breadth of the claims; (b) nature of the invention; (c) state of the prior art; (d) level of one of ordinary skill in the art; (e) level of predictability in the art; (f) amount of direction provided by the inventor; (g) existence of working examples; and (h) quantity of experimentation needed to make or use the invention based on the content of the disclosure. {See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986); and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988)}.

The above factors, regarding the present invention, are summarized as follows:

(a) *Breadth of the claims* - the breadth of the claims includes all of the tens of thousands of substituted pyrido[1,2-*a*]pyrazinones and pharmaceutical compositions of the formula I/II, shown right;



(b) *Nature of the invention* - the nature of the invention is evaluation of substituted pyrido[1,2-*a*]pyrazinones and pharmaceutical compositions of the formula I/II and the pharmacokinetic behavior of these substances in the human body as modulators of chemokine receptor activity;

(c) *State of the prior art* - *Nature Reviews: Drug Discovery* offers a snapshot of the state of the drug development art. Herein, drug development is stated to follow the widely accepted Ehrlich model which includes: 1) development of a broad synthetic organic chemistry program; 2) subsequent testing of compounds in an appropriate laboratory model for the disease to be treated; and 3) screening of compounds with low toxicity in prospective clinical trials (Jordan, V. C. *Nature Reviews: Drug Discovery,* 2, **2003**, 205);

(d) *Level of one of ordinary skill in the art* - the artisans synthesizing applicant's substituted pyrido[1,2-*a*]pyrazinones and pharmaceutical compositions of the formula I/II, where $j \neq 1$; $k \neq 1$; $A \neq -CH_2-$; $Y \neq -O-$; $R^1 \neq$ -H or $-C_{1-6}$alkyl; $R^5 \neq$ -H, -F, -Cl, -Br or $-C_{1-6}$alkyl; $R^6 \neq$ -H, -F, -Cl, -Br or $-C_{1-3}$alkyl; $R^{25} \neq$ -H or $-C_{1-6}$alkyl; $R^{26} \neq -(=O)$; m, n and X, together with the nitrogen to which they are attached, do not form a pyrrolyl ring; and any combination of R^7, R^8, R^9, R^{10}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33} and R^{34}, forms a ring, would be a collaborative team of synthetic chemists and/or health practitioners, possessing commensurate degree level and/or skill in the art, as well as several years of professional experience;

(e) *Level of predictability in the art* - Synthetic organic chemistry is quite unpredictable (See *In re Marzocchi and Horton* 169 USPQ at 367 ¶ 3). The following excerpt is taken from Dörwald, which has relevance to the synthesis of substituted pyrido[1,2-*a*]pyrazinones and pharmaceutical compositions of the formula I/II, where $j \neq 1$; $k \neq 1$; $A \neq -CH_2-$; $Y \neq -O-$; $R^1 \neq$ -H or $-C_{1-6}$alkyl; $R^5 \neq$ -H, -F, -Cl, -Br or $-C_{1-6}$alkyl; $R^6 \neq$ -H, -F, -Cl, -Br or $-C_{1-3}$alkyl; $R^{25} \neq$ -H or $-C_{1-6}$alkyl; $R^{26} \neq -(=O)$; m, n and X, together with the nitrogen to which they are attached, do not form a pyrrolyl ring; and any combination of R^7, R^8, R^9, R^{10}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33} and R^{34}, forms a ring (Dörwald, F. Zaragoza. *Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design*, Weinheim: WILEY-VCH Verlag GmbH & Co. KGaA, **2005**, Preface):

Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why.

Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.

Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious).

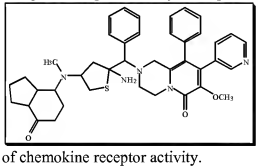
(f) *Amount of direction provided by the inventor* - the application is negligent regarding direction with respect to making and/or using substituted pyrido[1,2-*a*]pyrazinones and pharmaceutical compositions of the formula I/II, where $j \neq 1$; $k \neq 1$; $A \neq -CH_2-$; $Y \neq -O-$; $R^1 \neq$ -H or -C_{1-6}alkyl; $R^5 \neq$ -H, -F, -Cl, -Br or -C_{1-6}alkyl; $R^6 \neq$ -H, -F, -Cl, -Br or -C_{1-3}alkyl; $R^{25} \neq$ -H or -C_{1-6}alkyl; $R^{26} \neq$ -(=O); m, n and X, together with the nitrogen to which they are attached, do not form a pyrrolyl ring; and any combination of R^7, R^8, R^9, R^{10}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33} and R^{34}, forms a ring;

(g) *Existence of working examples* - applicant has provided sufficient guidance to make and/or use substituted pyrido[1,2-*a*]pyrazinones and pharmaceutical compositions of the formula I/II, where $j = 1$; $k = 1$; $A = -CH_2-$; $Y = -O-$; R^1 = -H or -C_{1-6}alkyl; R^5 = -H, -F, -Cl, -Br or -C_{1-6}alkyl; R^6 = -H, -F, -Cl, -Br or -C_{1-3}alkyl; R^{25} = -H or -C_{1-6}alkyl; R^{26} = -(=O); m, n and X, together with the nitrogen to which they are attached, form a pyrrolyl ring; and no combination of R^7, R^8, R^9, R^{10}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33} and R^{34}, forms a ring; however, the disclosure is insufficient to allow extrapolation of the limited examples to enable the scope of the tens of thousands of substituted pyrido[1,2-*a*]pyrazinones and pharmaceutical compositions of the formula I/II, where $j \neq 1$; $k \neq 1$; $A \neq -CH_2-$; $Y \neq -O-$; $R^1 \neq$ -H or -C_{1-6}alkyl; $R^5 \neq$ -H, -F, -Cl, -Br or -C_{1-6}alkyl; $R^6 \neq$ -H, -F, -Cl, -Br or -C_{1-3}alkyl; $R^{25} \neq$ -H or -C_{1-6}alkyl; $R^{26} \neq$ -(=O); m, n and X, together with the nitrogen to which they are attached, do not form a pyrrolyl ring; and any combination of R^7, R^8, R^9, R^{10}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33} and R^{34}, forms a ring. The specification lacks working examples of substituted pyrido[1,2-*a*]pyrazinones and pharmaceutical compositions of the

formula I/II, where $j \neq 1$; $k \neq 1$; A ≠ -CH_2-; Y ≠ -O-; R^1 ≠ -H or -C_{1-6}alkyl; R^5 ≠ -H, -F, -Cl, -Br or -C_{1-6}alkyl; R^6 ≠ -H, -F, -Cl, -Br or -C_{1-3}alkyl; R^{25} ≠ -H or -C_{1-6}alkyl; R^{26} ≠ -(=O); m, n and X, together with the nitrogen to which they are attached, do not form a pyrrolyl ring; and any combination of R^7, R^8, R^9, R^{10}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33} and R^{34}, forms a ring.

Within the specification, *specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. Markush claims must be provided with support in the disclosure for each member of the Markush group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula.* See MPEP § 608.01(p).

(h) *Quantity of experimentation needed to make or use the invention based on the content of the disclosure* - predicting whether a recited compound is in fact one that produces a desired physiological effect at a therapeutic concentration and with useful kinetics, is filled with experimental uncertainty, and without proper guidance, would involve a substantial amount of experimentation (Jordan, V. C. *Nature Reviews: Drug Discovery,* 2, **2003**, 205-213). Furthermore, it is unclear, based on the guidance provided by the specification, whether a substituted pyrido[1,2-*a*]-pyrazinone of the formula I/II, such as 2-((2-amino-4-(methyl(7-oxooctahydro-1*H*-inden-4-yl)amino)tetrahydrothiophen-2-yl)(phenyl)methyl)-7-methoxy-9-phenyl-8-(pyridin-3-yl)-3,4-dihydro-1*H*-pyrido[1,2-*a*]pyrazin-6(2*H*)-one, shown to the left, is either synthetically feasible or possesses utility in the human body as a modulator of chemokine receptor activity.



A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. {See *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)}.

The determination that *undue experimentation* would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion

reached by weighing all the above noted factual considerations. (See *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404). These factual considerations are discussed comprehensively in MPEP § 2164.08 (scope or breadth of the claims), § 2164.05(a) (nature of the invention and state of the prior art), § 2164.05(b) (level of one of ordinary skill), § 2164.03 (level of predictability in the art and amount of direction provided by the inventor), § 2164.02 (the existence of working examples) and § 2164.06 (quantity of experimentation needed to make or use the invention based on the content of the disclosure).

Based on a preponderance of the evidence presented herein, the conclusion that applicant is insufficiently enabled for making and/or using substituted pyrido[1,2-*a*]pyrazinones and pharmaceutical compositions of the formula I/II, where $j \neq 1$; $k \neq 1$; $A \neq -CH_2-$; $Y \neq -O-$; $R^1 \neq$ -H or -C_{1-6}alkyl; $R^5 \neq$ -H, -F, -Cl, -Br or -C_{1-6}alkyl; $R^6 \neq$ -H, -F, -Cl, -Br or -C_{1-3}alkyl; $R^{25} \neq$ -H or -C_{1-6}alkyl; $R^{26} \neq -(=O)$; m, n and X, together with the nitrogen to which they are attached, do not form a pyrrolyl ring; and any combination of R^7, R^8, R^9, R^{10}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33} and R^{34}, forms a ring, is clearly justified.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-22 and 24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation *or R^9 and R^{10} together are O, where O is connected to the ring via a double bond*, where the limitation is implausible, resulting in an incomplete valence.

Claims are unduly speculative where they define only a portion of a molecule. Consequently, since incomplete valences are not permitted in the structure of the substituted pyrido[1,2-*a*]-pyrazinones of the formula II, an essential portion of the molecule is indefinite and one of ordinary skill in the art, would not be reasonably apprised of the scope of the substituted pyrido[1,2-*a*]pyrazinones and pharmaceutical compositions of the formula II. {See *Ex parte Pedlow and Miner*, 90 USPQ 395 (Bd. Pat. App. & Int. 1951)}.

The examiner suggests replacing *together* with *independently*, to overcome this rejection.

Allowable Subject Matter

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DOUGLAS M. WILLIS, whose telephone number is 571-270-5757. The examiner can normally be reached on Monday thru Thursday from 8:00-6:00 EST. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DOUGLAS M WILLIS/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, AU 1624